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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,726	GRAHAM ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/8/09,10/7/09,10/13/09*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *134-157* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *134-157* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/8/09,5/8/09,5/8/09,10/13/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be to directed to Brian Whiteman, Art Unit 1635.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 134, 135, and 142-154 stand and claims 155-157 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter:

The claims are directed to methods for producing RNA capable of reducing expression of a target gene in a mammalian cell by administering a double stranded synthetic gene that comprises at least first and second structural genes, each of which

are 20-30 nucleotides in length. The claims are directed broadly any target gene within a mammalian cell.

Applicants point to page 10 as providing support for the limitation that the structural gene sequences are 20-30 nucleotides in length. However, this portion of the specification does not disclose use of structural genes of 20-30 nucleotides to target any gene, page 10 specifically states that structural genes of this length are a preferred embodiment targeting specific genes: viral DNA or RNA polymerases, viral coat proteins, or visually-detectable genes involved in determining pigmentation, cell death or other external phenotype. The generic disclosure of targeting any endogenous, foreign and viral genes is also found on page 10, but requires 30 contiguous nucleotides of the target.

Because the specification teaches that use of structural gene sequences of 20-30 nucleotides is limited to certain viral genes and visually detectable genes associated with external phenotypes, the disclosure of the specification is not commensurate in scope with the claimed invention and the claims do not satisfy the written description requirement.

Applicant's arguments filed 10/13/09 and 5/8/09 have been fully considered but they are not persuasive.

In response to applicant's argument that page 10 and pages 25 and 26 of priority application provides support for the claims and since in haec verba is not required there is support for the claims, the argument is not found persuasive because the skilled

artisan would not have ascertained the full scope of the claimed invention in view of the disclosure on page 10 and pages 25 and 26 of priority document.

"It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.,* 41 USPQ2d 1961, 1966 (CAFC 1997).

Claims 155 and 157 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Written description:

The claimed invention broadly reads on targeting a nucleotide sequence comprising 20-30 nucleotides or 20 consecutive nucleotides of a genus of visually-detectable gene. On page 15, lines 15-26, the specification recites:

> Preferred structural gene components of the synthetic gene of the invention comprise at least\about 20-30 nucleotides in length derived from a viral DNA polymerase, viral RNA polymerase, viral coat protein or visually-detectable gene, more particularly an RNA polymerase gene derived from a virus selected from the list comprising BEV, Sindbis alphavirus, HIV-I, bovine herpes virus and HSV1 or a visually-detectable gene which is involved in determining pigmentation, cell death or other external phenotype on a cell, tissue, organ or organism, amongst others.

> In a particularly preferred embodiment, the structural gene component of the synthetic gene comprises at least about 20-30 nucleotides in length derived from the BEV RNA-dependent RNA polymerase gene or the murine tyrosinase gene or the Escherichia coli lac repressor gene lacI or a complementary sequence thereto.

The specification does not define what is considered to be a visually-detectable gene. The specification describes expression constructs that contain full-length sequences from tyrosinase, GFP, and LacI gene and fragments 100-200 bases in length of tyrosinase. However, with respect to the limitation "visually detectable gene which is involved in determining pigmentation, cell death or other external phenotypes in a cell, tissue organ or organism," the specification does not provide a structure for what genes are embraced by these species. In view of the absence of a definition for the term in the specification and the different functions embraced by possibly each species there is a variation between species embraced by the genus recited in the claims. The prior art of record does not provide representative samples of the genus of sequences comprising 20-30 consecutive nucleotides or 20 consecutive nucleotides from a visually detectable gene. At the time of filing, neither the specification nor the art of record provide support for the skilled artisan to envision what genes are embraced by the claimed genus.

In order for the written description provision of 35 USC 112, first paragraph to be satisfied, applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed. For example, MPEP 2163 states in part,

> "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

The skilled artisan cannot envision the detailed structure of the encompassed genus of compounds that are structural gene sequences to a region of a target gene comprising about 20 nucleotides of a visually detectable gene, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Therefore, while the specification provides adequate description of constructs containing full-length sequences of tyrosinase, GFP and LacI genes, the full breadth of the many genes, known or unknown, and the many compounds that target gene comprising about 20 nucleotides of a visually detectable gene and reduce expression of the target gene that are encompassed by the claims do not meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Claim Rejections - 35 USC § 103

Claims 134-147 and 150-155 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (US 5,605,559, of record) in view of Agrawal et al. (WO 94/01550, of record), Gold et al. (US 5,270,163), Kotin et al. (US 5,580,703) and Chatterjee et al. (US 5,474,935, of record).

Fire et al. teach and claim a method of inhibiting gene expression in cells, including animal cells, using double stranded RNAs. The double stranded RNA comprises a sequence complementary to a portion of the target gene and a sequence identical to a portion of the target gene, each of which is at least 25 nucleotides. Target genes include cellular genes, endogenous genes, transgenes and viral genes (see claims 1-6 and 10). At column 4, lines 41-46 Fire et al. teach that dsRNAs used in the invention can be formed from a single self-complementary RNA. At columns 8-9 and in claim 21 Fire et al. teach that RNA synthesis can be initiated *in vivo* or *in vitro* and that RNA can be produced by an expression construct. Fire et al. additionally teach at column 9 that the dsRNA can be introduced to a cell in a variety of ways, including within a viral particle comprising a viral vector. At column 10 Fire et al. teach that viruses can be targeted. At column 5 Fire et al. teach that the dsRNA can target any gene and is not limited to any particular portion of the gene but do not explicitly teach targeting of the untranslated regions of a gene. Fire et al. do not explicitly claim the use of double stranded RNAs that comprise a stuffer fragment (i.e., a loop connecting the two portions of the RNA).

It was well known in the art at the time the invention was made that nucleic acids that are fully or partially self-complementary form hairpin structures having unpaired loop regions. For example, Agrawal et al. teach self-stabilized oligonucleotides comprising a target hybridizing region and a self-complementary region. On page 15 Agrawal et al. teach that the self-complementary region of the oligonucleotide is fully or partially complementary to the hybridizing region and may comprise an unpaired loop region. This concept is also exemplified by Gold et al., who teach in the drawings several RNAs with stem-loop structures. At column 24, Gold et al. teach that the RNAs of their invention can be amplified by any known means, including the use of vectors administered to a host cell.

At the time the invention was made it was known to those of ordinary skill in the art that some viral vectors can integrate an exogenous sequence into the genome of a cell. See, for example, Kotin et al., who teach that AAV vectors integrate site-specifically into a host's genome and that this characteristic can be exploited for gene therapy (see column 1, lines 15-20 and column 4, line 50 through column 5, line 2).

At the time the invention was made the person of ordinary skill in the art recognized that different regions of genes, including the untranslated regions, are suitable targets for nucleic acid therapeutics. Chatterjee et al. teach constructs targeted to viral genes, explicitly teaching that lentiviruses such as HIV and DNA viruses such as HSV are suitable targets, teaching at column 4 that any viral gene whose sequence is known can be targeted. One of ordinary skill in the art would recognize that this includes the genes for coat proteins and polymerases. At column 3 Chatterjee et al.

teach that antisense oligonucleotides targeted against areas of critical viral RNA transcripts including the 5'-untranslated region and splice sites (which are part of an exon) have demonstrated significant antiviral activities.

It would have been obvious to one of ordinary skill in the art at the time of invention to perform the method of inhibiting gene expression with double stranded RNA claimed by Fire et al. using a single self-complementary RNA formed by transcription of a synthetic gene sequence that comprises two copies of an RNA sequence in sense and antisense orientation and to use a sequence wherein each copy of the sequence is 20-30 nucleotides in length. Based on the claims of Fire et al. of using a duplex RNA that can comprise 25 nucleotides in each strand and can be produced from an expression construct, the teachings of Fire et al. that inhibitory double stranded RNA can be formed from a single self-complementary strand and the recognition by those in the art, as evidenced by Agrawal et al. and Gold et al., that self-complementary nucleotide strands form a hairpin comprising an unpaired loop, one of ordinary skill in the art would recognize the use of a hairpin RNA in place of a duplex of two strands and the size of the loop is a matter of design choice and that use of a hairpin RNA allows for production of the RNA within a cell from an expression construct. One would further recognize that because Fire et al. explicitly teach delivering an RNA to a cell using a viral vector and Kotin et al. teach that AAV vectors will integrate into a host's genome, the use of the vector taught by Kotin et al. is a matter of simple substitution of one known type of vector for another. It would have further been obvious to produce RNA targeted to a viral gene and to target the untranslated regions of the gene. Fire et al.

provide a motivation to target viral genes by specifically claiming such a target and Chatterjee et al. provide a motivation to target an untranslated region of a gene by teaching that targeting of such regions is proven to provide significant antiviral activity. Because the combination of the cited references provides a vector having the structural limitations of the claims and because administering this vector to a cell as taught by Fire et al. for the purpose of inhibiting gene expression would necessarily result in the production of a RNA capable of delaying, repressing or reducing expression of a target gene the invention of claims 134-155 would have been obvious, as a whole, at the time the invention was made.

Applicant's arguments filed 10/13/09 and 5/8/09 have been fully considered but they are not persuasive.

In response to applicant's argument that there was skepticism in the prior art about extrapolating the results observed in C. elegans to other organisms (see Wagner and Riggs, Nature 1998 (exhibit 18) and Riggs Declaration), the argument is not found persuasive because the Fire provisional contemplates using the dsRNA in mammalian cells, thus one of ordinary skill in the art would be motivated to try administering the dsRNA to mammalian cells. Fire taught that the introduction of dsRNA is at least 100-fold more effective than the injection of purified antisense RNA in inhibiting gene expression. Fire taught the use of viral vectors to deliver the dsRNA molecules in the cell. Furthermore, the present specification appears to only provide generic disclosure and no actual examples of inhibiting gene expression using the claimed construct in mammalian cells, which is similar to the teaching of Fire. The Declaration of David

Stalker teaches that at around the time the application was filed, one of ordinary skill in the art would have been motivated to try making dsRNA to inhibit a target gene in a cell if anything for practical research purposes.

In response to applicant's argument that the preferred route of administering the dsRNA is direct administration and not viral vectors, the argument is not found persuasive because one of ordinary skill in the art would have been motivated to use a vector for long-term expression of the dsRNA or for controlled expression of the dsRNA. "A reference may be relied upon for all that it would reasonably suggested to one having ordinary skill in the art, including nonpreferred embodiments." See Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert denied, 493 U.S. 975 (1989). Also see In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). Furthermore, applicant admitted that the routine procedure for transfecting animal cells with nucleic acid molecules to produce transiently or stably transfected animal cells were available prior to the filing date of the present invention (see pages 10 and 11 of the response filed on 11/14/00 in the application 09/100,812).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case because even though Agrawal, Gold, Chatterjee, and Kotin are not directed to gene silencing, Fire taken with Agrawal, Kotin, Chatterjee and Gold provide motivation for one of ordinary skill in the art to use the construct for expressing

each strand of the nucleotide sequence. Citing KSR, the Board stated that "when there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." See Ex parte Kubin, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007). The Declaration of David Stalker teaches that at around the time the application was filed, one of ordinary skill in the art would have been motivated to try making dsRNA based on the knowledge relating to antisense and ribozyme techniques has been well established by those dates.

In response to applicant's argument that the possibility of polyadenylation made it impossible to predict whether the claimed invention would successfully cause RNA interference, the argument is not found persuasive because the present specification appears to only provide generic disclosure and no actual examples of inhibiting gene expression using the claimed construct in mammalian cells, which is similar to the teaching of Fire. The instant claims do not require a polyadenylation tail for the product. In addition, if this was a cause for concern in the prior art, there are several promoters used in the prior art that do not result in polyadenylation of the product.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does

not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The Declaration under 37 CFR 1.132 filed on 10/13/09 is sufficient to overcome the 103(a) rejection of claims 134-154 based upon Fire taken with Agrawal, Gold, Kotin and Chatterjee.

Dr. Riggs has proposed several possible challenges the dsRNA may face in the nucleus. NOTE: the present specification does not appear to address these concerns by one skilled in the art (Dr. Riggs). Thus, these issues could also be directed to the instant claims.

The claimed invention only discusses a sequence or length in terms of DNA contained in vectors, never any length of RNA produced by such vectors; that even if the sequence contain only 20-30 nucleotides, this does not necessarily result in RNA transcripts having this same length. See Appeal Brief filed on 3/6/09 in application 10/805,804.

Furthermore, other than the generic contemplation in the specification, the working examples of the present application appear not to disclose using nucleotide sequence consisting of 20-30 nucleotides. Absence evidence to the contrary, the examples teach making construct comprising an open reading frame BEV polymerase gene, lacI gene, mRNA of the mouse tyrosinase cDNA or a fragment thereof (gene fragments of 100 to 200 base pairs in length).

In response to Dr. Riggs statement that Agrawal, Kotin, Chatterjee and Gold are not a reference from the gene silencing art and cannot be combined with Fire, the statement is not persuasive. First as mentioned by Dr. Riggs, using dsRNA to inhibit a target gene in a cell has never been reported before, thus there would be no prior art on the topic other than the teaching of Fire. It is acknowledged that Agrawal, Kotin, Chatterjee and Gold references are not directed to gene silencing, however, the references teach making and using nucleic acid inhibitors and method steps or products that were commonly used by one of ordinary skill in the art. Thus, one of ordinary skill would have been motivated to try combining prior art directed to using nucleic acid inhibitors with the cite references. See KSR vs. Teleflex, Id.

Dr. Riggs states that it is impossible to predict how the effects would be affected by changes made to the experimental system reported by Fire et al.

First, obviousness requires a reasonable expectation of success, but not absolute certainty. In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

As admitted by applicants (see pages 10 and 11 of the response filed on 11/14/00 in the application 09/100,812), it was routine for one of ordinary skill in the art at the time of filing to transfect animal cells with nucleic acid sequences to produce transiently or stably transfected animal cell. Furthermore, Fire discloses ex vivo or in vivo introduction of dsRNA into the cell of an organism for inhibiting gene expression. While it is agreed that at the time of filing that Fire did not know the mechanism (RNAi) that resulted in inhibiting expression of a target gene using dsRNA, the instant

specification was also unaware of the mechanism involved in inhibiting expression of a target gene using dsRNA encoded by a genetic construct. In view of the prior art of record, one of ordinary skill in the art would have been motivated to make and use a vector comprising the dsRNA for long-term or controlled expression of the dsRNA in mammalian cells compared to direct administration of the dsRNA to the cells.

Dr. Riggs states that shortest RNA with which Fire et al. observed was 299 base pairs longs and even though Fire discloses lengths from 25 to 400 base pairs corresponding to the target gene, the mechanism was unknown and one of ordinary skill in the art would not know the size requirement nor predict the consequence of decreasing the length of the RNA duplex (Exhibit 25).

The statement is not found persuasive because Fire teaches using lengths of RNA from 25 to 400 base pairs and the prior art (Manche) teaches that dsRNA longer than 30 base pairs induces a cellular immune response, thus providing motivation to try sequences below 30 base pairs, e.g., 25 base pairs and making a nucleotide sequence having 25 base pairs is cheaper than making a nucleotide sequence having 299 base pairs. Furthermore, the as-filed specification does not teach the mechanism that was supposedly lacking from Fire et al. Other than the instant specification contemplating and claiming the genetic constructs having at least 20-30 nucleotides of specific target genes or making the constructs in the working example, the teaching of the present application does not provide the mechanism of RNA interference and correlate what size operates in RNA interference that is lacking from Fire.

The statement is not found persuasive because the reference is a post-filing reference and the information disclosed by Tabara appears not to be issue before the filing of Fire et al. David Stalker indicates that one of ordinary skill in the art would have been motivated to investigate the possibility of using dsRNA molecules shorter than 299 base pairs.

Dr. Riggs states that except for the delivery of dsRNA to the gonads and the body cavity of C. elegans, all other delivery methods were untested and unpredictable.

The statement is not found persuasive because the prior art of record provides motivation and a reasonable expectation of success for administering a viral vector comprising the dsRNA to a mammalian cells. Obviousness requires a reasonable expectation of success, but not absolute certainty. In re O'Farrell, Id. Furthermore, the use of routine procedures for transfecting animal cells with nucleic acid molecules to produce transiently or stably transfected animal cells, taught by Fire taken with Agrawal, Gold, Kotin and Chatterjee would result in transcription of the sense and antisense strands in close proximity to each other thus ensuring favorable binding of the resulting duplex. Furthermore, Fire specifically taught “a viral vector packages into a viral particle would accomplish both efficient introduction of an expression vector into the cell and transcription of RNA encoded by the expression vector” (Fire provisional, page 12).

Dr. Riggs states that double-stranded RNA may not form in the nucleus (see Cameron et al., Nucleic Acid Research, 1991) and it would have been difficult to predict if the independent strands could form RNA duplexes in the nucleus to mediate gene silencing.

The statement is not found persuasive because Fire taught self-complementary can be used in the method and specifically taught "a viral vector packages into a viral particle would accomplish both efficient introduction of an expression vector into the cell and transcription of RNA encoded by the expression vector" (Fire provisional, page 12). Also see In re O'Farrell, Id.

Dr. Riggs Declaration refers to Okano (1991) in support of the argument that dsRNA may get trapped in the nucleus and it was possible that the dsRNA produced in the nucleus could suffer the same fate.

The statement is not found persuasive because Fire taught that the dsRNA-mediated inhibition showed an ability to cross cellular boundaries (see Fire provisional, page 20). The intracellular localization of the dsRNA transcribed by the DNA construct is determined by the type of vector and the design of the vector. The instant claims are not limited to transportation of the dsRNA transcribed by the DNA construct to the cytoplasm.

Dr. Riggs Declaration refers to Kumar et al., (Exhibit 19, 1998) in support of the argument that dsRNA may get modified in the nucleus and it could not have been predicted whether the effect of inosines would have on the system reported by Fire et al.

The statement is not found persuasive because the reference is a post-filing reference and the information disclosed by Kumar appears not to be an issue before the filing of Fire et al.

Dr. Riggs Declaration refers to Wu et al., (JBC, 1998, Exhibit 24) in support of the argument that dsRNA may get degraded in the nucleus and it could not have been predicted whether duplex structures would be degraded in the nucleus, thus compromising the double-stranded RNA and the ability to specifically silence gene as reported by Fire et al.

The Wu publication is after the filing date of Fire and appears to be unknown before the filing date of Fire et al. Thus, one of ordinary skill in the art would have been aware of the issue.

Dr. Riggs declares that polyadenylation at the 3' end of RNA may interfere with RNA interference (see Exhibits 21-23).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., inclusion of a poly-A tail) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, if polyadenylation at the 3' end of the RNA was a concerned by the skilled artisan, there are several well known promoters (e.g., bacteriophage T7 promoter) were polyadenylation does not occur in transcripts generated from it.

Dr. Riggs states that heterogenous nuclear ribonucleoproteins may affect double-stranded RNA formation Lodish (1999, Exhibit 21).

The statement is not found persuasive because the Lodish's reference is a post-filing reference which would have been unknown at the time Fire was filed.

Dr. Riggs states that claimed invention teaches the use of DNA constructs that would produce double-stranded RNA having a duplex region that has only 20-30 base pairs.

The statement is not found persuasive because the claimed invention only discusses a sequence or length in terms of DNA contained in vectors, never any length of RNA produced by such vectors; that even if the sequence contain only 20-30 nucleotides, this does not necessarily result in RNA transcripts having this same length. See Appeal Brief filed on application 10/805,804.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number 571-272-0764. The examiner can normally be reached on from 6:30 to 4:00 (Eastern Standard Time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor Tracy Vivlemore can be reached on 571-272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Brian Whiteman/
Primary Examiner, Art Unit 1635